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Inhalation Exposure System Used for Acute and Repeated-Dose Methyl Isocyanate Exposures of Laboratory Animals

by Bernard Adkins, Jr.,* Robert W. O'Connor,* and John M. Dement†

Laboratory animals were exposed by inhalation for 2 hr/day (acute) or 6 hr/day (four consecutive days, repeated dose) to methyl isocyanate (MIC). Exposures were conducted in stainless steel and glass inhalation exposure chambers placed in stainless steel, wire mesh cages. MIC was delivered with nitrogen via stainless steel and Teflon supply lines. Chamber concentrations ranged from 0 to 60 ppm and were monitored continuously with infrared spectrophotometers to 1 ppm and at 2-hr intervals to 20 ppb with a high performance liquid chromatograph equipped with a fluorescence detector. Other operational parameters monitored on a continuous basis included chamber temperature (20–27°C), relative humidity (31–64%), static (transmural) pressure (−0.3 in.), and flow (300–500 L/min). The computer-assistance system interfaced with the inhalation exposure laboratory is described in detail, including the analytical instrumentation calibration system used throughout this investigation.

Introduction

Methyl isocyanate (MIC) is an intermediate chemical used in the manufacturing of carbamate pesticides and other heterocyclic derivatives. Some physical properties of MIC are given in Table 1. MIC is categorized as an extremely hazardous chemical that is highly reactive, toxic, volatile, and flammable (*1*). Toxicological information is limited to two sources (*2*,*3*), which report MIC to be a poison by contact, oral ingestion, and inhalation. These reports summarize inhalation effects from exposure, including extreme irritation to mucous membranes (*2*), bronchospasm (with asthmalike breathing), and skin sensitization and cross reactivity to other isocyanates in rats and mice (*3*). MIC has not been reported to elicit skin sensitization in humans.

Table 1. Methyl isocyanate physical properties.[a]

Molecular weight	57.05
Apparent specific gravity at 20/20°C	0.9599
Boiling point at 760 mm Hg	39.1°C (102.4°F)
Vapor pressure at 20°C	348 mm Hg
Solubility in water at 20°C	ca. 6.7% by wt
Viscosity at 0°C	0.35 cP
at 20°C	0.25 cP
Heat of vaporization at 1 atm	223 Btu/lb
Heat of combustion at 25°C	8,041 Btu/lb
Flash point, closed cup	< 0°F

[a] From Union Carbide Corp (*1*).

The accidental release of MIC vapors in Bhopal, India, on December 3, 1984, prompted additional toxicological testing of this chemical. The purpose of the studies conducted at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC, was to characterize the toxicity of inhaled MIC in two species of laboratory animals, rats and mice, following single or multiple exposures to concentrations above and below the LC_{50}. Details on the inhalation exposure system, the generation and monitoring of MIC, the industrial hygiene sampling procedures, the monitoring of exposure environmental parameters, and the facility safety system employed for this study are described herein.

Materials and Methods

Chemical

The bulk stock of MIC was supplied in high-pressure stainless steel cylinders by Union Carbide (Agricultural Products Company, Inc., Research Triangle Park, NC). Vapor samples were collected for purity analysis and found to be >99% pure by flame ionization gas chromatography analysis (Radian Corporation, Research Triangle Park, NC). Cylinders were secured in a ventilated Plexiglas cabinet under negative pressure (−3.0 in. water). The cabinet contained a 2-inch bed of activated carbon as a safety precaution and was also

*Northrop Services, Inc., P.O. Box 12313, Research Triangle Park, NC 27709.
†National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709.

equipped with a glove port for ease of access and isolation of control valves (Fig. 1).

Data Acquisition and Storage System

A Digital Equipment Corporation (DEC, Maynard, MA) minicomputer (Model PDP-11/34) was used for exposure process control, data acquisition, and storage. The PDP-11/34 was equipped with 245 kbytes of random access memory, a digital input/output (I/O) interface, an analog-to-digital (A/D) converter, an eight-line serial interface, and RSX-11M V4.0 operating system. Software for this system was developed by Northrop Services, Inc. (Research Triangle Park, NC). Sampling frequency was present to once per second except for data from the infrared analyzers, which were sampled every 45 sec. Samples were collected less frequently with the infrared analyzer dedicated to the air control chamber and the dewpoint monitor, because these instruments were multiplexed between various sample sites. In the case of the control chamber analyzer, air samples were taken from the exposure laboratory and the effluent downstream from two exhaust scrubbers plumbed inline to handle MIC. The multiplexing was scheduled such that alternate readings were taken from the exposure room while the remaining sites were sampled in sequence. The dewpoint monitor (Model 911, EG&G, Waltham, MA) was multiplexed between the four inhalation exposure chambers in the laboratory.

The PDP-11/34 minicomputer was also used to acquire animal weight data. An electronic top-loading balance (Mettler Model PL3000, Hightstown, NJ) equipped with a binary coded decimal (BCD) interface was used for collecting animal weights. Each animal weighed was uniquely identified with a sequentially numbered stainless steel ear tag. Randomization software was used to distribute the parent population of animal weights into n groups such that each group had the same weight distribution as the parent population. An analysis of variance (ANOVA) was used to test for homogeneity. Once the animals were grouped, they were then randomly assigned to cages (ten mice/cage and four rats/cage).

Other computers available to this laboratory included a PDP-11/44 and a VAX-11/780. These computers were used for software development, data validation, data base management, and performing offline application tasks such as the randomization of tagged experimental animals.

Generation and Monitoring of MIC

Stainless steel and glass Rochester-type inhalation exposure chambers (1330 L) were used throughout this investigation. The inlet process air was conditioned with activated charcoal, filtered (high efficiency particulate absolute, HEPA), and temperature- and humidity-controlled.

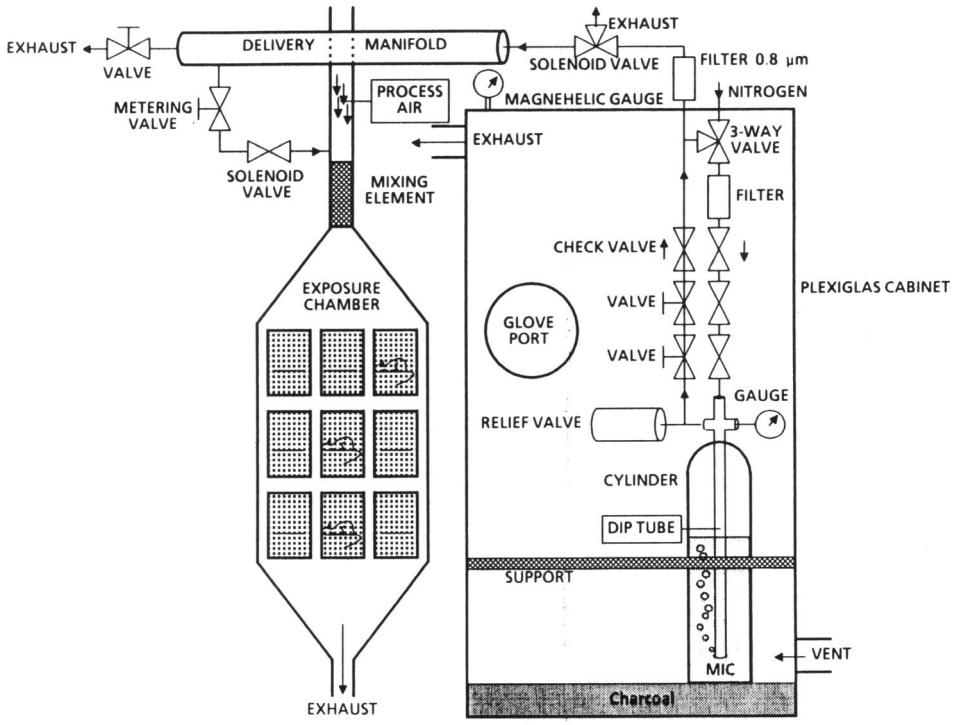

FIGURE 1. Flow diagram of the isolation chamber for stock methyl isocyanate and generation system associated with inhalation chambers used for laboratory animal exposures.

Dry, carrier-grade nitrogen (National Welding Supply, Raleigh, NC) was introduced into the MIC tank through a series of filters, shutoff valves, check valves, and a dip tube, as shown in Figure 1. The vapor was conducted from the tank through type 316 stainless steel lines to a stainless steel delivery manifold, which was isolated from the tank by an electronic, computer-controlled solenoid valve (3-way, Nacom, Tustin, CA). When activated, the three-way valve permitted pressurization of the delivery manifold and the metering valves (Hoke, Cresskill, NJ) used to control MIC delivery to each chamber. A "normally closed" electronic solenoid valve (Nacom) was used in conjunction with each metering valve to control the flow of the nitrogen-diluted MIC. The inlet to each exposure chamber was equipped with a convoluted, stainless steel, static mixing element (Koch, New York, NY), which was housed in the 2-inch, type 316, stainless steel inlet tube. The MIC was introduced into the process air stream, which then flowed through the mixing element and into the chamber.

The primary analytical technique used by this laboratory for monitoring MIC vapors was infrared spectroscopy. The Wilks Miran 80 infrared analyzer (Foxboro Analytical Instruments, Waltham, MA) was operated at a path length of 20.25 m. The analytical and reference wavelengths for MIC were approximately 3.3 and 3.6 μm, respectively. Any water interference at 3.3 μm was quantified with respect to the analytical wavelength for water (2.6 μm), and its effect was mathematically subtracted from the total absorbance measured at 3.3 μm. The lower detection limit for this analyzer in our system was determined to be 200 ppb. Averaging techniques inherent to the Miran 80 helped to reduce much of the background noise problem synonymous with infrared spectrophotometry, but contributed significantly to the lengthy (45-sec) equilibration and analysis time.

Calibration of the Miran 80 was accomplished by a matrix technique developed at NIEHS (*4,5*). This technique requires the acquisition of 10 seven-point curves that are computer-evaluated for homogeneity. If the 10 curves are determined to be homogeneous, regression coefficients are generated for up to a fourth-order polynomial fit. In addition to the 10-curve matrix, an additional seven-point calibration was performed daily and compared to the matrix to determine acceptability prior to the start of exposures.

In our system, chamber concentrations of MIC were automatically monitored and adjusted. This was accomplished through a feedback and control system. The chamber concentration was measured by using the Miran 80 linked to the PDP-11/34 (Fig. 2). These data were continuously compared to historical data and to the required set-point exposure concentration for the study. If the measured concentration was within 2% of the set point, no adjustments were made. If not, the computer adjusted the metering valve for the out-of-limits chamber. If the concentration returned to within normal limits, no further adjustments were made. If not, the computer continued to try to achieve the set point via further adjustment of the metering valve. If

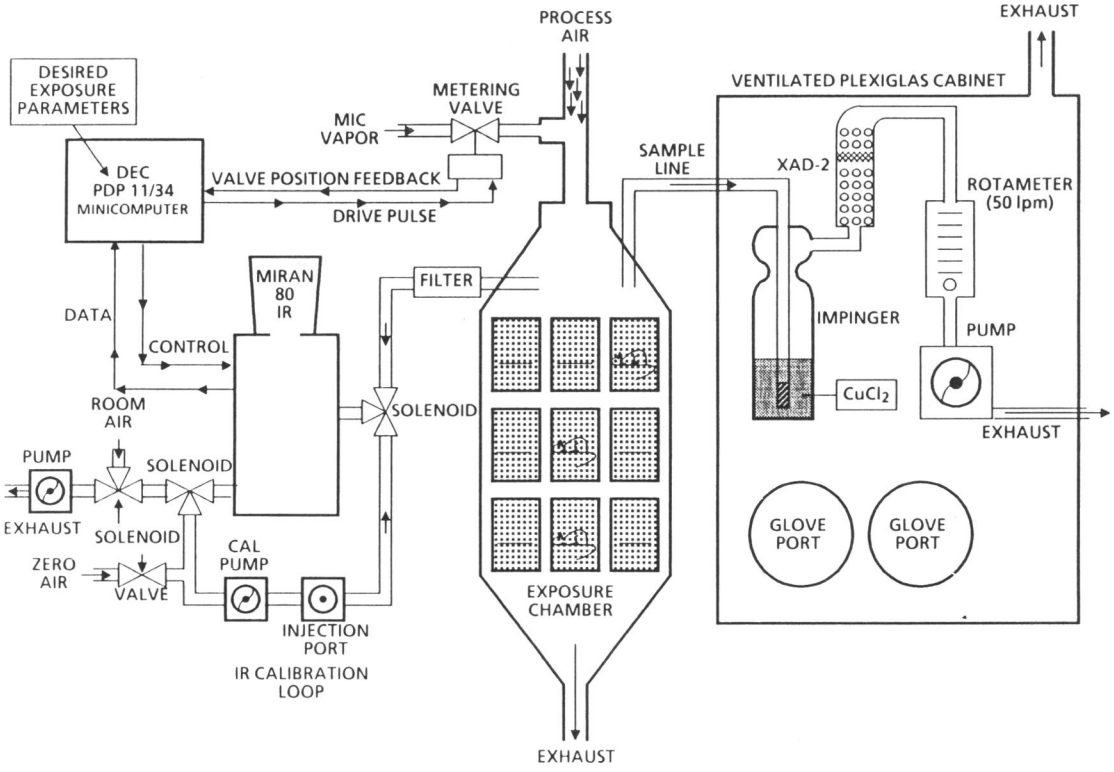

FIGURE 2. Flow diagram of IR and HPLC sampling system used for methyl isocyanate exposures and infrared calibration system.

the measured concentration was different from the set point by 10% or more, an alarm was sounded and manual input was required to correct the problem. If a 20% deviation was detected, the computer automatically terminated the flow of MIC and activated a second audible alarm, thus terminating the exposure. This complex algorithm also evaluated other operational parameters associated with the MIC exposure, including process air flow and static (transmural) pressure, which were similarly connected to the alarm systems.

Industrial Hygiene Monitoring

The American Conference of Government Industrial Hygienists (*6*) set a threshold limit value for MIC at 20 ppb. Since this level was an order of magnitude lower than the minimum detection level for the Miran 80, a high performance liquid chromatograph (HPLC, Waters Model 780, Milford, MA), equipped with a Model 420 fluorescence detector, was used to achieve more sensitivity. The detector used a General Electric F4T5.D lamp, a bandpass excitation filter with a center frequency of 395 nm, and a longpass emission filter with a cutoff of 455 nm. The HPLC analysis was performed on MIC-fluorescent adducts (fluorescamine, fluram; Hoffmann-LaRoche, Inc., Nutley, NJ) following tetrahydrofuran (Fisher Scientific Co., Fair Lawn, NJ) elution of the air samples taken at 2-hr intervals on XAD-2 resin (amberlite, Supelco; Bellefonte, PA) (*7*). Safety considerations included monitoring the exposure laboratory and effluent downstream from the charcoal scrubbers for the presence of MIC as well as ventilating the exposure chambers for a minimum interval of 45 min after each exposure prior to unloading exposed animals. A training program was conducted for all personnel prior to initiation of testing, and full-face respirators with external air supply (Willson, Reading, PA), butyl rubber gloves, and full Tyvek suits (Fisher Scientific, Raleigh, NC) were provided at all times for personnel entering the laboratory during exposures.

Environmental Monitoring and Control System

In addition to chamber MIC concentrations, ambient temperature, dewpoint temperature, static (transmural) pressure, process air flow, and barometric pressure were also measured. These end points were measured once per second during a 5-min period. At the end of each 5-min interval, the data were evaluated, and the mean, standard deviation, maximum and minimum values, and the number of data points collected were stored on magnetic media. The dewpoint monitor was multiplexed between the four chambers in the exposure laboratory, resulting in the recording of the 5-min sample only once per hour. All effluents from the chambers and Plexiglas cabinets passed through bag-in/bag-out scrubbers containing Type CG whetlerized activated carbon (Barnebey Chaney, Columbus, OH).

Results

MIC Generation System

A flow diagram of the generation system used to expose laboratory animals to MIC vapor is presented in Figure 1. An expanded view of the isolation chamber used to contain the stock MIC is presented in relation to the exposure chamber shown. Also, only one exposure chamber is shown plumbed into the delivery manifold for descriptive purposes; the actual laboratory contained four chambers attached to the manifold and peripheral equipment.

Exposure Monitoring and Data Acquisition and Storage Systems

A flow diagram of the infrared (IR) analyzer and HPLC sampling systems and the process control and data acquisition systems used throughout this investigation are presented in Figure 2. Functional components of the calibration loop assembly associated with one IR analyzer are shown. An expanded view of the components of the overall inhalation exposure system are presented in relation to the exposure chamber shown. The exposure laboratory contained four exposure chambers with four independent IR analyzers and calibration systems. Sampling lines from each exposure chamber were plumbed to the ventilated Plexiglas cabinet in a manner shown in Figure 2.

Inhalation exposures were typically started when the actual chamber concentrations monitored by the IR analyzers were consistently above background noise and showed a positive slope. The T90 for our system with the MIC was typically 12 min. Target concentrations were typically achieved within 30 min of the actual start of the inhalation exposures.

Table 2 summarizes the MIC exposure concentrations for all exposures conducted during these studies. These data indicate the accuracy and precision of the generation and monitoring system previously described. It is noteworthy that many of the 1-ppm exposures had to be conducted via manual override with regards to the automatic operation of typical exposures due to high background noise experienced with this exposure level and the lower detection limit of the Miran 80 IR analyzers. Exposures were conducted at all concentrations reported within approximately $\pm 10\%$ of the set-point concentrations.

Problems encountered during the conduct of this study categorized as one of three types. First, calibrations with liquid MIC were not only difficult to perform, but also difficult to reproduce. The problem involved withdrawing 0.2-μL samples of liquid MIC with a 10-μL syringe, which required reading the syringe accurately and preventing the MIC from vaporizing in the syringe needle during injection into the calibration system. This problem was not adequately resolved until a static dilution system was developed and incorporated into our system (Fig. 2). The volume of the calibration

Table 2. Summary of methyl isocyanate inhalation exposure chamber concentrations determined during acute and repeated dose studies with rats and mice.[a]

	Nominal MIC exposure concentration[b]				
Exposure date (1985)	1 ppm	3 ppm	10 ppm	20 ppm	30 ppm
03–11	1.00 ± 0.22[b] (62) [0.72, 1.38]	2.96 ± 0.22 (63) [2.35, 3.42]	N/D[c]	N/D	N/D
03-12	0.99 ± 0.19 (65) [0.60, 1.49]	2.61 ± 0.88 (66) [0.00, 3.61]	N/D	N/D	N/D
03-13	1.00 ± 0.32 (66) [0.30, 1.70]	2.92 ± 0.61 (65) [0.62, 3.65]	N/D	N/D	N/D
03-14	0.97 ± 0.26 (66) [0.30, 1.24]	3.02 ± 0.26 (66) [2.62, 3.62]	N/D	N/D	N/D
03-27	N/D	3.03 ± 0.28 (20) [2.36, 3.62]	9.76 ± 0.46 (18) [8.80, 10.52]	N/D	30.07 ± 0.51 (19) [29.16, 31.46]
04-11	1.07 ± 0.05 (66) [0.96, 1.15]	2.95 ± 0.34 (67) [1.38, 3.38]	N/D	N/D	N/D
04-12	0.92 ± 0.08 (64) [0.79, 1.16]	2.97 ± 0.54 (64) [2.48, 4.43]	N/D	N/D	N/D
04-13	1.01 ± 0.05 (65) [0.84, 1.09]	3.06 ± 0.31 (66) [2.52, 3.82]	N/D	N/D	N/D
04-14	1.04 ± 0.07 (66) [0.95, 1.23]	3.01 ± 0.18 (66) [2.72, 3.60]	N/D	N/D	N/D
04-22	N/D	3.26 ± 0.43 (18) [2.66, 4.75]	9.23 ± 1.46 (18) [7.92, 10.92]	N/D	28.84 ± 1.59 (18) [27.31, 31.37]
04-29	N/D	2.95 ± 0.46 (18) [2.58, 4.08]	9.48 ± 1.43 (18) [8.22, 13.00]	N/D	29.96 ± 3.31 (18) [22.44, 35.36]
05-30	N/D	2.52 ± 0.79 (18) [0.76, 3.58]	8.88 ± 0.48 (18) [7.94, 9.66]	18.95 ± 0.63 (18) [17.95, 20.34]	N/D
05-30				19.27 ± 0.78 (17) [17.25, 20.21]	
06-05	N/D	N/D	N/D	N/D	29.96 ± 2.49 (18) [22.65, 34.23]
06-11		2.28 ± 0.55 (17) [1.35, 3.57]	9.83 ± 0.44 (17) [9.16, 10.63]	N/D	29.03 ± 0.74 (17) [27.95, 30.26]

Table continues on following page.

system was designed such that the total volume withdrawn for use was < 1% of the total volume of the calibration loop. This latter improvement produced very accurate and reproducible calibrations.

The second problem encountered involved a white crystalline residue found throughout the delivery system. This residue slowly clogged pressure regulators, metering valves, and the supply line in the bulk stock cylinder. These deposits caused irregular vapor flow, which in turn contributed to the instability in chamber concentrations, particularly at the lower exposure levels. The only solution to this problem was regular cleaning of all affected parts with absolute methanol. Samples of this residue were taken for gas chromatograph mass spectral analysis and were found to contain three principal components: 1,3-dimethylurea, MIC trimer, and 1,3,5-trimethylbiuret. Formation of this last residue is probably related to the extreme reactivity of MIC with water, iron, and other trace materials that occur in the type of delivery system used for this study. Since the components of the residue are similar to those found in the underground MIC storage tank in Bhopal, India, following the disaster of December 3, 1984, as reported by Heylin (*8*), we can only speculate that the dry, carrier-grade nitrogen used in our generation system may have contained some water.

The third problem involved background noise associated with the Miran 80 IR analyzers with the path length set at 20.25. At this maximum sensitivity, the noise was quantified to equate to approximately 200 ppb MIC, which affected exposure control at the 1- and 3-ppm levels. This last problem did not allow for

Table 2. Continued.

Exposure date (1985)	Nominal MIC exposure concentration[b]				
	1 ppm	3 ppm	10 ppm	20 ppm	30 ppm
06-17	1.15 ± 0.36 (66) [0.00, 1.69]	2.99 ± 0.28 (66) [1.95, 3.34]	N/D	N/D	N/D
06-18	0.95 ± 0.26 (65) [0.12, 1.48]	2.50 ± 0.63 (65) [0.63, 3.42]	N/D	N/D	N/D
06-19	1.15 ± 0.21 (66) [0.40, 1.62]	2.79 ± 0.41 (66) [1.37, 3.65]	N/D	N/D	N/D
06-20	1.27 ± 0.11 (66) [1.04, 1.66]	2.87 ± 0.30 (66) [1.74, 3.42]	N/D	N/D	N/D
06-25	1.04 ± 0.16 (66) [0.52, 1.49]	2.90 ± 0.28 (66) [1.73, 3.45]	N/D	N/D	N/D
06-26	1.15 ± 0.12 (65) [0.90, 1.44]	2.99 ± 0.25 (65) [2.27, 3.39]	N/D	N/D	N/D
06-27	1.19 ± 0.17 (66) [0.69, 1.54]	3.04 ± 0.11 (66) [2.79, 3.27]	N/D	N/D	N/D
06-28	1.12 ± 0.17 (66) [0.57, 1.53]	2.97 ± 0.21 (66) [2.21, 3.42]	N/D	N/D	N/D
07-10	0.87 ± 0.36 (18) [0.29, 1.45]	2.95 ± 0.34 (18) [2.28, 3.33]	9.21 ± 1.62 (19) [3.63, 11.13]	N/D	N/D
07-10	0.98 ± 0.41 (17) [0.30, 1.89]		8.86 ± 0.99 (18) [6.61, 10.17]		
09-23	0.93 ± 0.41 (64) [0.30, 2.19]	2.87 ± 0.51 (64) [0.83, 3.39]	N/D	N/D	N/D
09-24	0.88 ± 0.32 (65) [0.56, 2.06]	2.91 ± 0.34 (65) [1.81, 3.54]	N/D	N/D	N/D
09-25	0.87 ± 0.15 (66) [0.48, 1.63]	3.01 ± 0.35 (66) [1.84, 3.53]	N/D	N/D	N/D
09-26	1.00 ± 0.25 (65) [0.52, 1.81]	2.81 ± 0.48 (65) [1.42, 3.76]	N/D	N/D	N/D

[a] Nominal MIC exposures were conducted at 6 ppm on 9-23, 9-24, 9-25, and 9-26 with actual concentrations of 5.92 ± 1.61 (64, 3.74, 17.54), 5.97 ± 0.67 (65, 2.82, 6.72), 5.83 ± 0.41 (66, 4.73, 6.75), and 5.59 ± 1.52 (65, 0.48, 12.67), respectively. A nominal exposure was conducted at 60 ppm on 6-5 with an actual concentration of 57.48 ± 1.68 (18, 54.10, 60.84).

[b] Data presented as mean ± SD for exposure period; numbers in parentheses represent number of data points; numbers in brackets represent minimum and maximum data points observed during exposure period, respectively.

[c] N/D, not done.

the automatic operation of all of these exposures and required manual input, especially at the 1-ppm exposure level.

Industrial Hygiene Monitoring

Results from all HPLC analyses indicated an absence of any detectable MIC in the exposure laboratory air, the air control exposure chamber, and the effluent downstream from the two Type CG whetlerized activated carbon scrubbers. Since the lower detection limit of the HPLC in our system was 20 ppb, these results substantiate the effectiveness of the safety precautions taken during this study.

Environmental Monitoring and Control System

Environmental parameters monitored during this study included ambient temperature, which ranged from 20 to 27°C; relative humidity, which ranged from 31 to 64%; and transmural pressure, flow and barometric pressure, which were observed to be well within the normal operating range for these parameters for this laboratory. It is noteworthy that the Type CG whetlerized activated carbon scrubbers in our system were changed monthly, which is more frequently than recommended by the manufacturer. The expended activated carbon cells were double-bagged and incinerated.

Discussion

Over a period of five months, two types of inhalation exposures of rats and mice to MIC vapors ranging from 0 to 60 ppm for either 2 or 6 hr/day were conducted. This experimental design required that the inhalation exposure system be state-of-the-art and have "real time" monitoring of exposures to assess accurately the toxicological insult of the inhalation of MIC vapor on the primary target organ, the respiratory system, as well as potential effects systemically. Since numerous other toxicological studies were to be conducted with these animals, including genetic toxicity, immunotoxicological, and reproductive/developmental toxicity studies, this requirement became of paramount importance.

Several facility renovations were made prior to the start of the actual exposures. These activities mainly included installation of additional alarms and/or systems designed for added personnel safety. Since there were no leaks during our studies, these systems were not activated, but may be useful to others performing toxicological studies with MIC or other highly toxic chemicals.

Additionally, the computer-assisted process control and data management system associated with our inhalation exposure facility functioned well considering the reproducibility and low variability of the exposure data presented in Table 1. It is noteworthy that our generation and monitoring systems differed from those used previously by Kimmerle and Eben (*2*) and Pozzani and Kinkead (*3*), in which either evaporation or atomization generation systems and either spectrophotometric wet chemistry or gas chromatography flame ionization detection systems were used, respectively.

Operational problems encountered with our generation and delivery system were traced to a residue formation. This problem may have been avoided with the incorporation of a drying agent downstream from the nitrogen. Elimination of this type of problem should allow duplication of this effort and the successful administration of other highly toxic chemicals for inhalation toxicology investigations.

The results and procedures presented in this report are in support of a series of toxicological studies, the results of which are presented separately. The procedures described are considered appropriate for conducting toxicity studies on highly toxic chemicals. The tightness of the chamber exposure data and the lack of human operator exposure or effluent discharge confirm the high quality and accuracy of procedures used in these animal studies.

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